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Sleep Spindles Are Related to Schizotypal Personality Traits and Thalamic Glutamine/Glutamate in Healthy Subjects

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Background: **Schizophrenia is a severe mental disorder affecting approximately 1% of the worldwide population. Yet, schizophrenia-like experiences (schizotypy) are very common in the healthy population, indicating a continuum between normal mental functioning and the psychosis found in schizophrenic patients. A continuum between schizotypy and schizophrenia would be supported if they share the same neurobiological origin. Two such neurobiological markers of schizophrenia are: (1) a reduction of sleep spindles (12–15 Hz oscillations during nonrapid eye movement sleep), likely reflecting deficits in thalamocortical circuits and (2) increased glutamine and glutamate (Glx) levels in the thalamus. Thus, this study aimed to investigate whether sleep spindles and Glx levels are related to schizotypal personality traits in healthy subjects.** ***Methods:*** **Twenty young male subjects underwent 2 all-night sleep electroencephalography recordings (128 electrodes). Sleep spindles were detected automatically. After those 2 nights, thalamic Glx levels were measured by magnetic resonance spectroscopy. Subjects completed a magical ideation scale to assess schizotypy.** ***Results:*** **Sleep spindle density was negatively correlated with magical ideation ($r = -.64$, $P < .01$) and thalamic Glx levels ($r = -.70$, $P < .005$). No correlation was found between Glx levels in the thalamus and magical ideation ($r = .12$, $P > .1$).** ***Conclusions:*** **The common relationship of sleep spindle density with schizotypy and thalamic Glx levels indicates a neurobiological overlap between nonclinical schizotypy and schizophrenia. Thus, sleep spindle density and magical ideation may reflect the anatomy and efficiency of the thalamo-cortical system that shows pronounced impairment in patients with schizophrenia.**

Key words: sleep EEG/magical ideation/magnetic resonance spectroscopy/thalamo-cortical connections/schizophrenia/continuum model

Introduction

Schizophrenia is a multifaceted neuropsychiatric disorder that affects approximately 1% of the worldwide population.[1] However, a growing body of evidence suggests that there is a considerably higher incidence of psychosis-like signs (eg, delusion-like beliefs) in nonclinical populations, a characteristic commonly referred to as schizotypy or psychosis proneness.[2]

A psychosis continuum entails that symptoms observable in psychotic disorders (eg, schizophrenia) can be obtained in nonclinical populations and that the presence of psychosis- like symptoms are not necessarily bound to the presence of the disorder.[2] This theory is supported by studies reporting that schizotypal personality traits and schizophrenia may share common genetic and neurobehavioral features.[3–5] Thus, several studies provide evidence for a genetic continuity between schizophrenia and nonclinical schizotypy.[3,6] For example, Vollema et al[3] demonstrated that biological-genetic vulnerability to schizophrenia was associated with the positive dimension of a schizotypy questionnaire. Other studies showed that relatives of schizophrenia patients score higher on schizotypy scales than subjects without familial risk.[6] In addition, an overlap between schizotypy and schizophrenia was reported in neurocognitive measures that are deficient in patients with schizophrenia. For instance, right hemispatial inattention, a neurocognitive deficit

frequently observed in schizophrenia, was associated with schizophrenia-like experience and beliefs in healthy young male students.[7–9] In these studies, the magical ideation scale was used to assess quantitatively a person's proneness to schizophrenia-like experience and thoughts (positive dimension of schizotypy).[10] Therefore, the continuum of magical ideation is psychometrically relevant even for completely healthy subjects. Nevertheless, for schizotypy to represent an attenuated form of psychosis it would need to have the same neurobiological basis. Apart from testing the continuum model, exploring the neurobiological origin of psychosis-like signs in healthy subjects may further contribute to the elucidation of the neurobiological mechanism and anatomical structures underlying psychosis. In addition, investigations in subclinical groups may foster the search for the most sensitive neurophysiological and behavioral spectrum markers for schizophrenia. Finally, it is often difficult to distinguish whether an aberrant neurobiological marker in schizophrenic patients is a primary cause of the disease or a result of medication or disease history. Thus, studies in healthy subjects may help to overcome this difficulty.

Based on several findings, schizophrenia has been conceptualized as a network disorder mediated by abnormal brain connectivity and disrupted neuronal communication.[11,12] In particular, thalamo-cortical deficits have been reported in schizophrenia.[11,13,14] The sleep spindle, a thalamo-cortically generated phasic oscillation between 12–15 Hz during nonrapid eye movement (NREM) sleep, putatively reflects anatomical and functional differences of the thalamo-cortical system.[15,16] Patients with schizophrenia show a remarkable decrease in sleep spindles, likely reflecting deficits in thalamo-cortical circuits.[17–19] Therefore, sleep spindles are thought to be an electrophysiological marker for the integrity of the thalamo-cortical system. Moreover, Ferrarelli et al[17] reported a 90% separation of schizophrenic patents and healthy subjects based on spindle measures. Collectively, sleep spindles seem to be a promising neurobiological spectrum marker of schizophrenia.

Increased glutamine (Gln) and glutamate (Glu) levels (sum of both denoted as Glx) in the thalamus and the anterior cingulate have also been found in medicated and nonmedicated patients with schizophrenia and subjects at high risk for schizophrenia.[20–22] Thus, altered brain glutamatergic transmission (eg, disinhibition of Glu release in the cortex) is proposed as a primary neurochemical marker for schizophrenia.[23] Pharmacological models) of schizophrenia can be obtained by noncompetitive *N*-methyl-D-aspartate (NMDA) receptor glutamatergic antagonists (eg, ketamine), which affect behavior and induce schizophrenia-like manifestations in animal models and humans.[24] These models provide evidence that abnormal glutamatergic transmission might be caused by NMDA receptor blockage in GABAergic interneurons in the thalamus that leads to a disinhibition of Glu release in the cortex.[25,26] Because these thalamo-cortical circuits are also involved in the spindle generation and synchronization, Glu levels in the thalamus may be related to sleep spindles and schizotypal personality traits.

Assuming that delusion-like beliefs and schizophrenia-like experiences in healthy subjects may have the same neurobiological origin as in patients with schizophrenia, our study aimed to investigate whether sleep spindles are associated with thalamic Glx levels in healthy volunteers, and whether Glx levels and sleep spindles are related to magical ideation.

Methods

Participants

Twenty healthy male subjects (age: 23.3 ± 2.1 years; mean ± *SD*) were recruited by advertisement at the University of Zurich and ETH Zurich. Only male subjects were included because in female subjects spindle activity varies systematically across the menstrual cycle.[27] Participants with family history of psychopathology, chronic diseases, current use of psychoactive agents, or other medications were excluded (telephone and questionnaire screening). Furthermore, we applied the schizotypal personality questionnaire[28] in German[29] to exclude subjects at high risk for schizotypal personality disorder. The scores of all subjects were in the normal or even lower range (standardized values: −1.1 ± 0.64 *SD*. Norm values provided by Klein 1999, unpublished work, $n = 649$ male healthy young adults). Thus, none of our subjects was at a higher risk for schizotypal personality disorder. They were further nonsmokers and right handed. All subjects were normal, healthy sleepers as verified with a screening night (sleep efficiency >80%). To ensure stable conditions, subjects were required to maintain a regular sleep-wake schedule (8-h time in bed, according to scheduled bedtime in the lab) and to abstain from caffeine, naps, and alcohol 3 days before the study nights. Compliance was controlled by breath alcohol test, wrist-worn actometers, and sleep logs. The procedures were approved by the cantonal ethic commission in Zurich, Switzerland, and the study was performed according to the Declaration of Helsinki. All participants gave written informed consent to participate in the experiment.

Procedure

Each participant underwent 2 study nights 2 weeks apart with bedtimes either at 2250–0650 or 2340–0740. All-night high-density electroencephalography (EEG) was recorded during both nights. Subjects underwent a magnetic resonance spectroscopy measurement 11.0 ± 8.2 days after the second study night and completed a magical ideation scale.

Polysomnography

High density EEG 128 electrodes,[30] electrooculogram and submental electromyogram were continuously recorded

during the 8-h night-time sleep episode. The signals were digitized at 500 Hz (filters: 0.01–200 Hz), referenced to Cz. For further analysis, the EEG was band-pass filtered (0.5–40 Hz) and resampled at 128 Hz.

The sleep stages were scored for 20-s epochs according to standard criteria[31] and artifacts were identified on a 20-s basis by visual inspection and a semiautomatic procedure. The data were re-referenced to the average reference of all good quality EEG channels above the ears (109; of these, on average, seven channels per subject were of insufficient quality). Thereafter, for topographical analysis, spindle values (see "Spindle Detection" section) of bad channels were interpolated using a spherical interpolation provided by EEGLAB toolbox.[32]

Spindle Detection

Sleep spindle detection was performed according to the detection algorithm of Ferrarelli et al.[17] We thereby focused on the first hour of artifact-free NREM sleep. We selected this time interval because it includes the same number of epochs for all subjects and belongs to the most consolidated part of sleep. In short, the EEG signal was band-pass filtered between 12 and 15 Hz. A sleep spindle was detected in the rectified signal if the signal amplitude exceeded an upper threshold that was defined relative to the mean signal amplitude. An upper threshold of five times the mean signal was determined to result in the best spindle detection after visual inspection of spindle density values that were comparable with previous studies.[33,34] Beginning and end of sleep spindles were set when the signal around the peak amplitude dropped below a lower threshold (two times the mean signal). We focused our analysis on sleep spindle density (number per min NREM sleep), because this measure is one of the most affected in patients with schizophrenia.[18,19] An illustration of an EEG trace with detected sleep spindles is shown in supplementary figure 2 and averaged spindle density number in supplementary figure 1. Using this algorithm with the specific thresholds, the number of detected sleep spindles per time (density) was comparable with several other studies[33,35–37] (density at C4 [average referenced EEG]: 3.8921 ± 0.265 spindles per min). So far no "gold standard" for spindle detection is available. This is also supported by the fact that reported spindle density values and the chosen detection algorithms vary across studies.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) studies were performed with a 3 T GE HDxt MRI scanner (GE Medical Systems) equipped with TwinSpeed gradients. Single voxel 1H MR spectra were acquired from a $20 \times 20 \times 20\,mm^3$ voxel of interest positioned in the left thalamus as done in earlier studies[20,21,38,39] using a Point RESolved Spectroscopy sequence with an echo time (TE) of 35 ms and a repetition time (TR) of 3 s. The left thalamus was chosen to avoid chemical shift displacement artifacts, which may result in unwanted excitation of the water in ventricular cerebrospinal fluid (CSF), outside the prescribed voxel. Sixty-four spectral averages were acquired for each spectrum using an eight-channel receive-only head coil, resulting in an acquisition time of 4 min (illustrative spectra and the selected voxel of the thalamus can be found in supplementary figure 3). The scan protocol also included structural imaging (T1, T2, and DTI). T1-weighted images were acquired with a 3D fast inversion-recovery prepared spoiled gradient acquisition in the steady state (IR-SPGR), with inversion time (TI) = 600 ms, TE = 4.25 ms, TR = 11.4 ms, flip angle = 8°, and an isotropic voxel resolution of 1 mm, used for localization of the spectroscopy voxels. The volumetric IR-SPGR images were segmented into gray matter (GM), white matter (WM), and CSF maps using statistical parametric mapping (SPM8, Wellcome Department of Cognitive Neurology) to correct the spectroscopy results for partial volume CSF contamination.

Total scan time was 25 min. Subjects were told to stay awake during the whole scan procedure. We spoke to the subjects between each scan to verify that they were still awake. They all confirmed that they did not fall asleep during these MRS scans or before.

Water scaled metabolite concentrations were derived with the LC Model version 6.2-4.[40] Each MR-spectrum was visually inspected for the presence of artifacts or fitting errors. Poorly fitted metabolite peaks (Cramer-Rao minimum variance bounds of more than 10% for Cre or *N*-acetyl aspartate or more than 20% for any of the other metabolites) and spectra with visible artifacts were excluded from further analysis. For the included spectra, the average signal to noise ratio was 19.2 (±3.4 *SD*) and the linewidth 5.9 Hz (±0.8 *SD*). Owing to the tight spectral overlap between Glu and Gln at 3 T,[39,41] the sum of both, Glx, was used to investigate the link between Glu levels, spindle rhythms, and schizotypy. The concentrations were corrected for partial volume contamination of CSF,[42] using the correction factor given in Chowdhury et al.[43] To control for differences in the fractions of GM and WM within the voxel we covaried in an additional analysis for the GM/WM fraction[43,44] in a partial correlation design.

Schizotypal Properties

We used an adapted version of the magical ideation scale developed by Eckblad and Chapman,[10] which is a validated questionnaire commonly used to asses proneness to schizophrenia-like experience and thoughts (indicator for schizotypy or schizophrenia-proneness). This questionnaire originally consisted of 30 true/false questions, of which we selected 10 specific questions (items 4, 11, 15, 19, 20, 24, 25, 27, 28, and 30; English version of the scale

printed in full in Eckblad and Chapman[10]). This selection was based on an item-total correlation analysis ($n > 1000$) of the original questionnaire[10] whereby all single items were correlated to the sum of the others. We selected the 10 items with the highest correlation coefficients, because high item-total correlation values contribute more to a scale's reliability and may be considered more representative of the concept "magical ideation" than low item-total correlation values (unpublished data provided by Dr. Peter Brugger). Instead of true/false answers subjects had a six-point rating scale for each question ranging from "strongly disagree" (0 points) to "strongly agree" (5 points). This rating scale allows a more fine-tuned assessment of magical thinking. Scores of the 10 questions were added and a higher total score (maximal 50 points) represents a more distinct occurrence of schizophrenia-like experiences and beliefs.

Of note, this adapted version of the Eckblad and Chapman[10] questionnaire was not validated so far. The more fine-tuned scale is difficult to compare with the "yes/no" questions of the original Eckblad and Chapman[10] scale. To approximate this "yes/no" type of answers, we additionally rated a question as a "yes" if the subject scored ≥3 and as a "no" if the subject scored <3.

Statistics

All spindle values were averaged for both study nights to obtain more stable spindle measures. Pearson correlations were used to assess relationships between sleep spindle measures, schizotypal properties, and Glx levels in the left thalamus. Topographical distributions of r values are shown for correlations including the spindle measures. For topographical analysis, we applied statistical nonparametric mapping using a suprathreshold cluster analysis to control for multiple comparisons and to define specific regions of interest.[18,45] Thus, the neighboring electrodes that were above/below a significant r value of .54/−.54 (corresponding to a P value of .025 for $n = 17$, Bonferroni controlled P value for 2 correlation topographies) and exceeded the 90th percentile cluster size given by the permutation analysis were considered significant and included in further analysis (regions of interests). Correlations of these specific regions of interest (illustrated in the scatter plots) were considered significant with P values < .05. For the sleep spindle measures, one subject had to be excluded due to bad sleep and data quality. Two subjects were excluded from MRS analysis due to poor MR-spectrum quality. One subject did not complete the questionnaire and one subject was a correlation outlier with a questionnaire score that was more than 2.5 times the *SD* above the mean (30 points). The number of subjects included in the correlation analysis is provided in the respective figures.

Results

In the magical ideation questionnaire, our subjects ($n = 20$) reached on average 10 points (±7 *SD*, out of 50 points) and answered 1.74 questions (±1.79 *SD*) with "yes" (range of questions scored with "yes" is 0–6 out of 10 questions). Chmielewski et al[46] provided norm data for the Eckblad and Chapman[10] scale for white male students ($n = 3112$). Their subject answered on average 30.3% of the questions with "yes," in our sample only 17.9% of the questions were answered with "yes." As the number of questions differs between the original and the adapted assessment tool (30 vs 10 questions), this value is difficult to compare but seems to be lower than the norm. According to Eckblad and Chapman,[10] subjects that scored 2 *SD* above the mean (4.4% of all participants) were rated to be at higher risk for psychosis. In our study, only one subject was clearly deviant from the mean (60% of the questions answered with "yes," 30 of 50 possible points on the fine-tuned scale) and a correlation outlier, and was therefore not included in the correlation analysis.

We first explored the relationship between sleep spindle density in the frequency range of 12–15 Hz with magical ideation and thalamic Glx levels (figure 1). To control for multiple comparisons, only neighboring frequency bins that demonstrated pronounced regional clustering of significant correlations with both magical ideation and Glx levels in the thalamus were considered for further analysis (red rectangles in figure 1, q.v. supplementary figure 1 for spindle density distribution). Visual inspection revealed pronounced clusters of correlations between magical ideation/thalamic Glx and sleep spindle density in the 14.25–14.75 Hz range (three 0.25-Hz bins; figure 1). Based on these results, we further investigated the topographical distribution of the relationship (correlation) between spindle density in the frequency range of 14.25–14.75 Hz and magical ideation, and thalamic Glx levels, respectively. Magical ideation, a marker for a person's proneness to schizophrenia-like experience and thoughts, was negatively correlated with spindle density in a widespread cluster of centro-parietal electrodes (figure 2A), with the highest R^2 value reaching .46. These correlations even persisted when using the adapted "yes/no" score (see "Methods" section, data not shown).

In addition, higher thalamic Glx were associated with lower spindle density levels for a right parieto-temporal cluster (figure 2B). In this cluster, the highest R^2 value was .59. Although approximately half of the investigated voxel contains thalamic structure, it is clear that other subcortical areas are also included within the voxel (q.v. supplementary figure 3). Thus, in an additional analysis we also included the GM/WM ratio (0.49 ± 0.12) as a covariate in our correlation to test whether differences in tissue fraction may account for the observed relationship between Glx and sleep spindles (supplementary figure 4). The results were comparable to those obtained without applying the GM/WM fraction as a covariate (highest R^2 value was .58 for partial correlation).

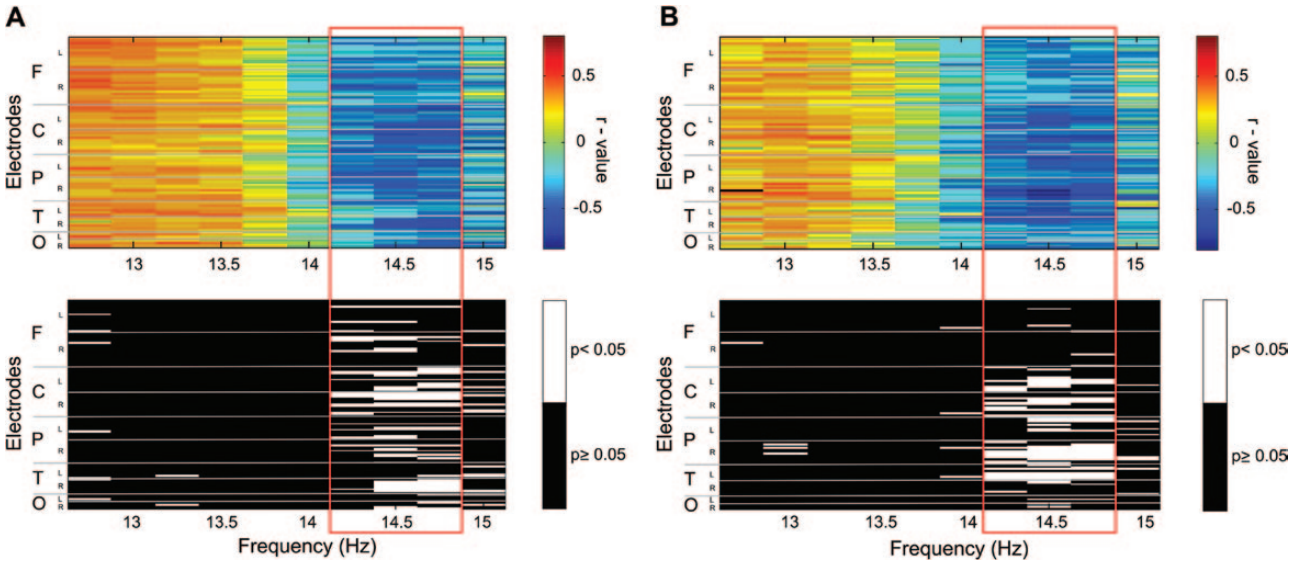

Fig. 1. Fast spindle density is inversely correlated with magical ideation and thalamic glutamine and glutamate (Glx) levels. Heat plots of the correlation coefficients and corresponding statistics for the relationship between spindle density of the first hour of nonrapid eye movement sleep and (A) magical ideation score ($n = 17$); (B) thalamic Glx levels corrected for CSF ($n = 17$). The x-axis represents the frequency bins where sleep spindles were detected by our algorithm (supplementary figures 1 and 2). The y-axis indicates the 109 high density EEG electrodes grouped into sets of electrodes that were close in distance to the 10–20 system configuration. F, frontal; C, central; P, parietal; T, temporal; O, occipital; L, left; and R, right. The red rectangle highlights the frequency bins that showed significant (white bars, $P < .05$) correlations over pronounced clusters of electrodes.

Finally, we investigated the relation between Glx level in the thalamus and magical ideation and observed no significant correlation between these 2 measures (figure 3).

Discussion

In this study, we combined for the first time high-density sleep EEG and MRS measures of Glx to investigate neurobiological correlates of schizotypy. We found that fast sleep spindle density was inversely related with magical ideation and thalamic Glx.

Reduced sleep spindling (eg, density and power) has been reported in schizophrenia.[17–19] Thus, the negative relationship between magical ideation, which reflects the proneness to delusion like beliefs, and sleep spindle density is consistent with previous findings in patients with schizophrenia. Importantly, we found this relationship in healthy young subjects that do not suffer from schizophrenia or schizotypal personality disorder, implying that schizophrenia-like perceptual experiences in healthy and psychotic symptoms in patients with schizophrenia seem to overlap at the neurobiological level. This finding supports the continuum model suggesting that unusual but nonclinical beliefs may represent a milder form of the clinical delusions found in severe mental illness.[2] This line of research provides evidence that schizotypal personality traits and schizophrenia may share common genetic, neurophysiological, neurocognitive, and neurobiological features.[3–5,47] To date only very few studies investigated the neurobiological overlap between schizophrenia and schizotypy.[5,47] Corlett and Fletcher[5] were able to relate schizotypy to neuronal responses in an associative learning task. They reported in healthy subjects a negative correlation between magical ideation and fronto-striatal prediction error signal, which describes the mismatch between what we expect and what we experience in a given situation, measured with functional magnetic resonance imaging. Importantly, a disrupted dorsolateral prefrontal prediction error signal was also found in patients suffering from psychotic illness.[48] The investigation of neurobiological overlap between schizophrenia and nonclinical schizotypy is important to disentangle neural mechanism and underlying structures that are involved in the generation of psychosis. Both sleep spindles and magical ideation may depend on the anatomy and efficiency of the thalamo-cortical system, eg, the number, strength, and myelinisation of thalamo-cortical fibers.[49,50] The reticular nucleus of the thalamus is the generator of sleep spindles[51,52] and plays a significant role in sensory input gating, processing, and filtering of information.[53] Schizophrenics are thought to be overwhelmed with information and stimuli due to deficient thalamo-reticular circuits that may lead to delusion and hallucination.[13,54] Thus, anatomical and functional variations of the thalamus are likely reflected in differences in sensory gating and filtering of information and stimuli that may or may not lead to schizophrenia-like perceptual experiences. Collectively, fast sleep spindle density seems to be a promising and sensitive spectrum marker for schizophrenia. Moreover, our findings indicate that sleep spindle

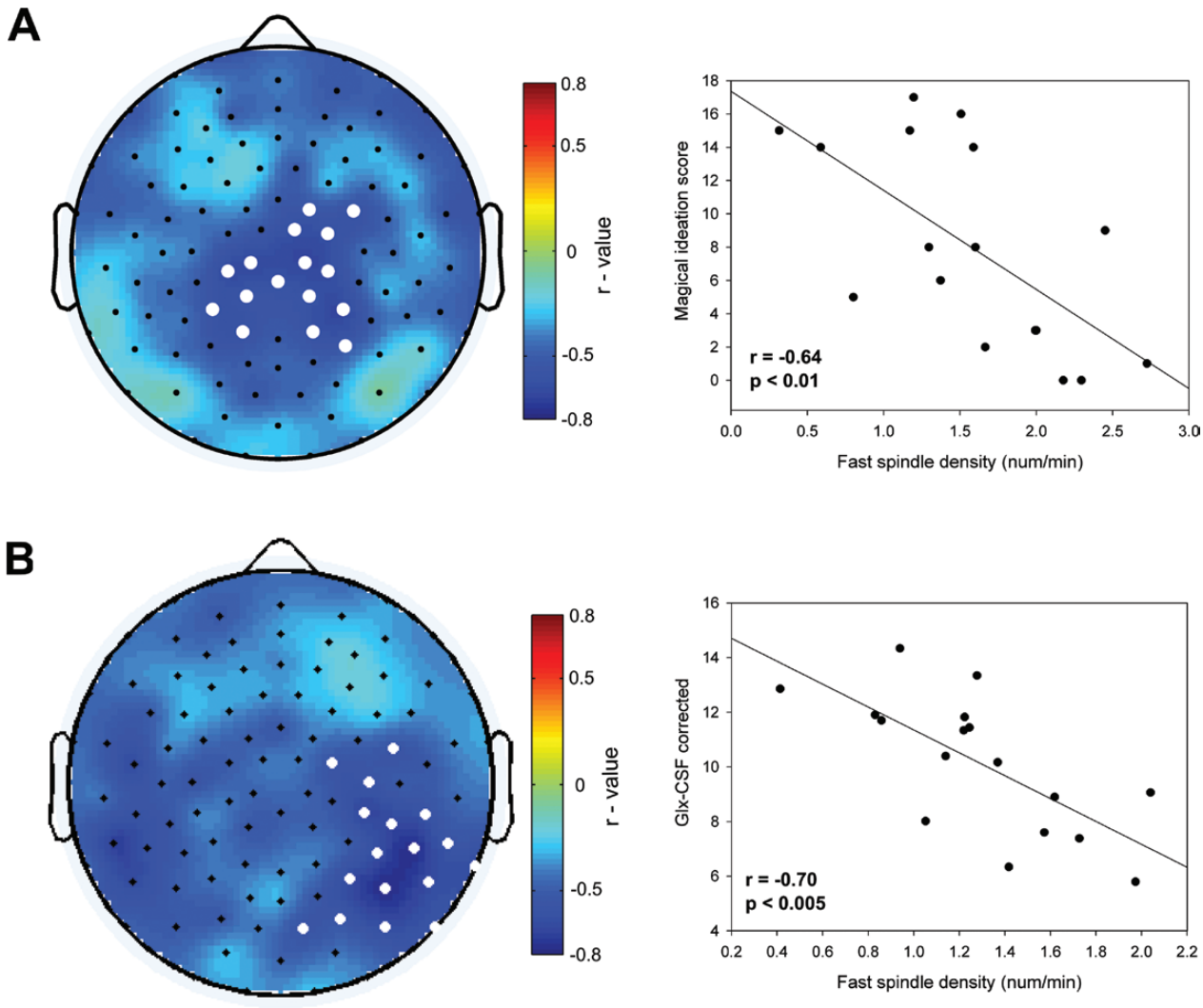

Fig. 2. Illustration of the correlation between fast spindle density (14.25–14.75 Hz) and (A) magical ideation score (n = 17), and (B) thalamic glutamine and glutamate levels corrected for CSF (n = 17). Topographical distribution of r values is plotted on the planar projection of the hemispheric scalp model with negative correlations reflected in blue. White dots indicate significant electrode clusters after controlling for multiple comparisons. The scatter plots further demonstrate the significant correlation for the highlighted electrode clusters.

deficits and therefore thalamo-cortical aberrations seem to be a primary marker for schizophrenia, because the relationship in healthy subjects is not confounded by medication or history of disease.

Our data further revealed that fast spindle density was negatively correlated with thalamic Glx. This relationship in healthy subjects is in line with the observation that patients with schizophrenia and subjects at high risk for this illness show increased thalamic Glx. Of note, when comparing the results of the present study to those of previous studies it is important to take into account the different thalamic voxel sizes employed. The voxel used in the present study also included nonthalamic subcortical structures (q.v. supplementary figure 3). However, even when we controlled for potential differences in voxel composition (covaried for GM/WM fraction)[12,13] in an additional partial correlation analysis the results were comparable to those obtained without applying the GM/WM fraction as a covariate.

Most thalamic afferents and efferents in the thalamus are glutamatergic and have a functional role in modulating thalamic activity during wakefulness and sleep.[55] In combination with other neurotransmitters, Glu can facilitate the transition of the thalamic system from sleep to wakefulness and consequently from a rhythmic burst mode to a tonic single spike mode.[55] The thalamo-cortical system is responsible for sleep spindle generation whereby thalamo-reticular neurons that fire in the burst-spike mode trigger sleep spindles.[56] Thus, increased thalamic Glx levels during sleep may reflect more activating inputs to the thalamus (brainstem and/or cortical) that suppresses rhythmic burst firing of the thalamus

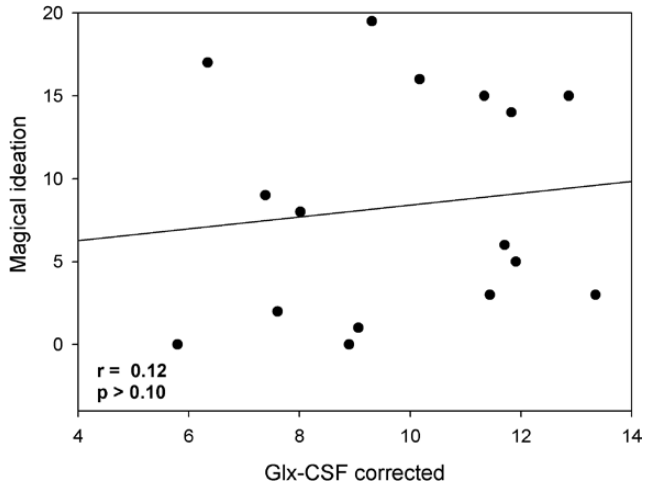

Fig. 3. Correlation between thalamic glutamine and glutamate levels corrected for CSF and the magical ideation score was not significant ($n = 16$).

and therefore reduce the generation of sleep spindles. In the present study, the participants were awake during the MRS measurements; therefore, we do not know the Glx levels during sleep and are further unable to distinguish the origin of the apparent increase in Glx levels in participants scoring high in magical ideation. Another interesting explanation could be that subjects with high thalamic Glx levels (in the awake state) were more aroused in wakefulness and that this tendency toward hyperarousal carried over to the sleep state. However, we were not able to relate the thalamic Glx levels to signs of arousal during sleep (eg, wake after sleep onset or sleep depth).

Increased thalamic Glx may result from several different processes (eg, increased glutamatergic release or less reuptake of Glu) and Glx levels reflect the changes of both Glu and Gln.[57] There is evidence that 80%–100% of the Glu that is released as a neurotransmitter at the synapse is directly cycled to Gln in the astrocytes, such that Gln levels might reflect the degree of Glu release at a specific region, eg, thalamus.[21,58] However, in addition to Glu playing an important role in neurotransmission, it also is involved in metabolic processes. Moreover, the MRS visible Glx signal includes both pools of Glu as well as Gln. Therefore, the Glx concentration measured with MRS may not provide a direct measurement of excitatory neurotransmission.

Interestingly, MRS studies performed at 4 T, which provides clear separation of Gln and Glu peaks, mainly found increased thalamic Gln in schizophrenic patients, which might point to an increased Glu release in the thalamus.[20,21,58] Moreover, the MRS visible Glx signal includes both intra- and extracellular pools of Glu as well as Gln. However, due to the overlap of Glu and Gln at 3 T, we are unable to separate Glu and Gln levels in our study. Although well-fitted Glu values were derived from the MR spectra in all subjects, Gln was not well-fitted in many subjects, suggesting that in these cases the apparent Glu values may be contaminated with Gln. For this reason, Glx was selected as a more consistent measurement of Glu across all participants. Admittedly, the hypothesized biological mechanism explaining the relationship between thalamic Glx and the sleep spindles remains speculative and further studies are needed to disentangle the underlying mechanisms. Nevertheless, compelling evidence exists that deficient glutamatergic neurotransmission and spindle generation are found in schizophrenic patients.[17,18,20–22,25,26,39] As mentioned in the "Introduction" section, abnormal glutamatergic transmission might be caused by NMDA receptor blockage on GABAergic interneurons in the thalamus.[25,26] Thus, Glx levels and sleep spindle density might be tightly coupled through the thalamic system.

Although a negative relationship between sleep spindle density and magical ideation/Glx levels was evident over the whole cortex, this correlation only reached significance in central or parieto-temporal electrodes and the correlation was further restricted to the high spindle frequency range (14.25–14.75 Hz). Ferrarelli et al[18] demonstrated that the effect size in spindle measure differences between patients and schizophrenia was most pronounced for spindle number (which is related to density) and integrated spindle activity (comprising a combination of spindle parameters). When focusing on the first hour of NREM sleep, Ferrarelli et al[17] described a spindle reduction (eg, power, number) in schizophrenics that was, at least for the power, also restricted to the high frequency range (13.75–15.00 Hz) and to a central cluster. Cortical topography of sleep spindles demonstrate that the majority of sleep spindles over centro-parietal regions are around 14 Hz, whereas slow spindles around 12 Hz[15] are most pronounced over frontal regions, thus possibly explaining why the correlation in our specific regions was restricted to the high spindle frequency range. Interpretation of these regions should be done cautiously because we cannot directly deduce underlying source of spindle activity from cortical EEG topography, especially because subcortical regions like the thalamus are involved in its generation. In addition, visually inspecting the topographical distribution of correlation coefficients indicates that the effect is rather global. Thus, we belief the emerging cluster in the right hemisphere is to some extent dependent on statistical power and the possible meaning of the region that reaches significance should not be overestimated.

Finally, thalamic Glx did not predict magical ideation. Therefore, sleep spindle density seems to be a more sensitive marker for schizotypal personality traits, at least in healthy subjects. Tandon et al[22] reported a significant positive correlation between Glx levels in the thalamus with measure of schizotypy in subject at high familial risk for schizophrenia, but none in healthy control subjects. It is possible that subjects showing extreme/high values of

schizotypy and thalamic Glx levels would show a significant correlation.

Our findings need to be considered in the context of several methodological limitations. Some adaptations and differences of the methods (EEG, MRS, and magical ideation scale) compared with other studies were implemented for an optimization to our data and experimental design. Especially for the MRS measurements, different factors might have influenced our data. More specifically, even though carefully controlling for CSF and partial gray to white matter ratio, some of the voxels selected might have been derived from different brain regions than the thalamus.

Furthermore, our results should be considered in the context of a relatively small number of subjects that may not be representative of typical control values. Thus, a larger study would help define the normal variation.

Finally, whether our findings might apply to high risk subjects is unclear because our healthy subjects scored below the norm of magical ideation. Thus, future studies should investigate these relationships in subjects with schizotypal personality disorder or relatives of schizophrenic patients.

In conclusion, our results support the notion that schizophrenia-like experiences possibly exists as a part of a continuum and depend on the same neurobiological system as psychotic experiences in schizophrenia. Thus, sleep spindle density and magical ideation may reflect the anatomy and efficiency of the thalamo-cortical system that shows pronounced impairment in patients with schizophrenia. In the future, sleep spindle measures might be used as objective markers for schizophrenia. In addition, nonclinical groups seem to be ideally suited to elucidate the neurobiological origin of schizophrenia-like behavior not confounded by therapy and disease history.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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